Formulation And Evaluation of Immediate Release of Cenobamate

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***Abstract*—The present study was aimed at the formulation and evaluation of immediate release tablets of Cenobamate, an antiepileptic drug, to achieve rapid onset of action and improved patient compliance. A total of nine formulations (F1–F9) were prepared by direct compression method using different concentrations of super disintegrants. All the prepared formulations were subjected to pre-compression and post-compression evaluation parameters, which were found to be within the acceptable limits as per the Indian Pharmacopoeia (IP) specifications. Among the formulations, F6 exhibited superior performance with rapid disintegration time, acceptable hardness, friability, and uniform drug content, along with enhanced in vitro drug release profile compared to other formulations. Thus, F6 was identified as the optimized formulation, demonstrating its potential for the development of an effective immediate release dosage form of Cenobamate.**

***Index Terms*—Cenobamate, Immediate Release Tablets.**

I. INTRODUCTION

Oral route is the most convenient and extensively used for drug administration. Oral administration is the most popular route for systemic effects due to its ease of ingestion, pain, avoidance, versatility and most importantly, patient compliance suitable for industrial production, improved stability and bioavailability. The concept of immediate release tablets emerged from the desire to provide patient with more conventional means of taking their medication when emergency treatment is required. Recently, immediate release tablets have gained prominence of being new drug delivery systems. The oral route of administration has so far received the maximum attention with respect to research on physiological and drug constraints as well as design and testing of product, Drug delivery systems (DDS) are a strategic tool for expanding markets/indications, extending product life cycles and generating opportunities. Most immediate release tablets are intended to disintegrate in the stomach, where the pH is acidic. Several orally disintegrating tablet (ODT) technologies based on direct compression. In pharmaceutical formulation includes any formulation in which the rate of release of drug from the formulation is at least 70% (preferably 80%) of active ingredient within 4 hours, such as within 3 hours, preferably 2 hours, more preferably within 1.5 hours, and especially within an hour (such as within 30 minutes) of administration. In Formulation of immediate release the commonly Superdisintegrants used are Croscarmellose, sodium, Sodium Starch glycolate and Crospovidone. Oral route of administration is the most popular route for systemic effects due to its ease of ingestion, pain, avoidance, versatility and most importantly, patient compliance. Also solid oral delivery systems does not need sterile conditions and are therefore, less expensive to manufacture. Patient compliance, high precision dosing, and manufacturing efficiency make tablets the solid dosage form of choice. There is requirement for new oral drug delivery system because of poor patient acceptance for invasive methods, requirement for investigation of new market for drugs and combined with high cost of disease management. Developing new drug delivery techniques and that utilizing in product development is critical for pharma companies to survive this century.

The term ‘immediate release’ pharmaceutical formulation is the formulation in which the rate of release of drug and/or the absorption of drug from the formulation, is neither appreciably, nor intentionally, retarded by galenic manipulations. Immediate release

dosage form is those which break down quickly and get dissolved to release the medicaments. In the present case, immediate release may be provided of an appropriate pharmaceutically acceptable diluent or carrier, which diluent or carrier does not delay, to an appreciable extent, the rate of drug release and/or absorption.

Immediate release drug delivery is suitable for drugs having long biological half-life, high bioavailability, lower clearance and lower elimination half-life. But main requirement for immediate release dosage form is poor solubility of the drug and need the immediate action of drug to treat undesirable imperfection or disease.

1.1 Pharmacokinetics:

It is the study of absorption, distribution, metabolism and excretion. After absorption, drug attains therapeutic level and therefore elicits pharmacological effect, so both rate and extend of absorption is important. In conventional dosage form there is delay in disintegration and therefore dissolution is fast. Drug distribution depends on many factors like tissue permeability, perfusion rate, binding of drug to tissue, disease state, drug interaction etc. Duration and intensity of action depends upon rate of drug removal from the body or site of action i.e. biotransformation. Decrease in liver volume, regional blood flow to liver reduces the biotransformation of drug through oxidation, reduction and hydrolysis. Excretion by renal clearance is slowed, thus half-life of renal excreted drugs increase.

1.2 Pharmacodynamics:

- ✓ Drug reception interaction impaired in elderly as well as in young adult due to undue development of organ.
- ✓ Decreased ability of the body to respond reflexive stimuli, cardiac output, and orthostatic hypotension may see in taking antihypertensive like prazosin.
- ✓ Decreased sensitivity of the CVS to α-adrenergic agonist and antagonist.
- ✓ Immunity is less and taken into consideration while administered antibiotics.
- ✓ Altered response to drug therapy-elderly show diminished bronchodilator effect of theophylline
- ✓ shows increased sensitivity to barbiturates.

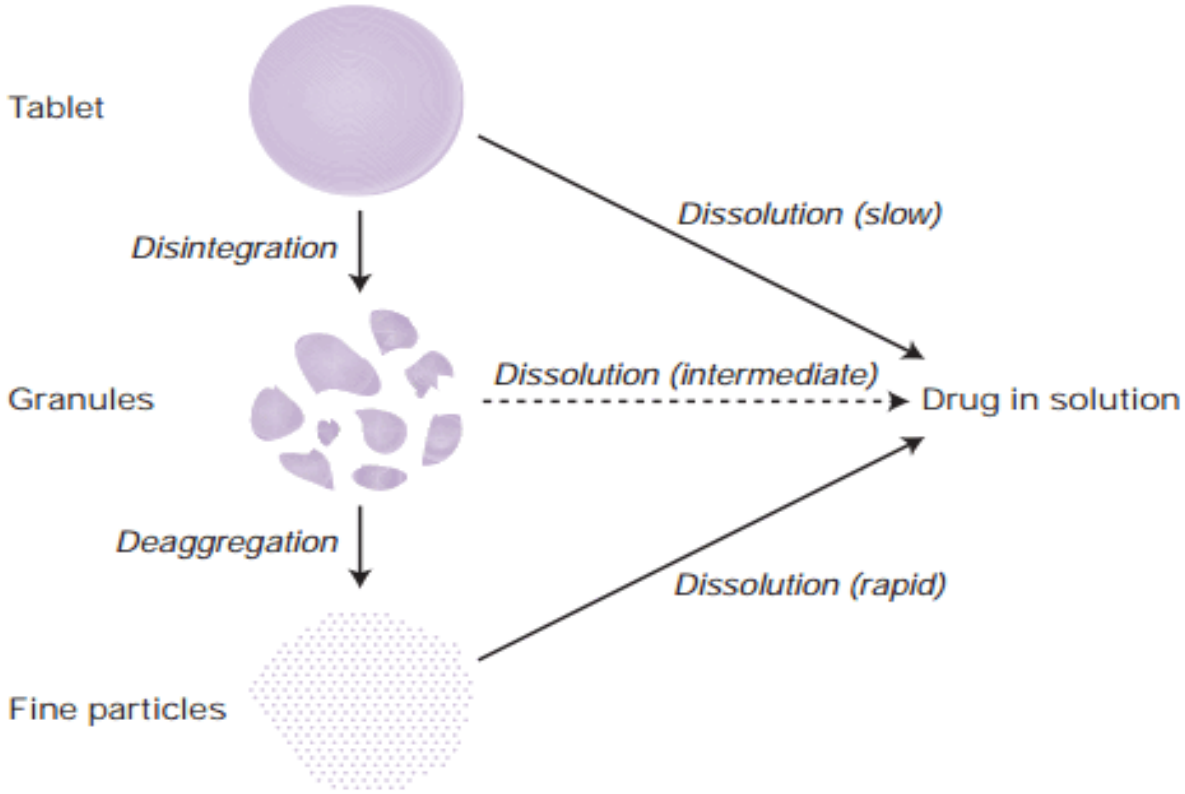


Fig 1.1: Drug release and dissolution process of an oral tablet

1.3 Type and Classes of Tablets:

1.3.A. Oral Tablets for Ingestion

- ✓ Compressed tablets
- ✓ Multiple compressed tablets
- ✓ Layered tablets
- ✓ Compression-coated tablets
- ✓ Repeat-action tablets
- ✓ Delayed-action and enteric-coated tablets
- ✓ Sugar and chocolate-coated tablets
- ✓ Film coated tablets

1.3.B. Tablets Used in the Oral Cavity

- ✓ Buccal tablets
- ✓ Sublingual tablets
- ✓ Troches and lozenges
- ✓ Dental cones

1.3.C. Tablets Administered by Other Routes

- ✓ Implantation tablets
- ✓ Vaginal tablets

1.3.D. Tablets Used to Prepare Solutions

- ✓ Effervescent tablets
- ✓ Dispensing tablets
- ✓ Hypodermic tablets
- ✓ Tablet triturates

1.4 Merits:

1. Unit dose system and Long shelf life.
2. Cost effective.
3. Improved stability, bioavailability.
4. Accuracy and uniformity of drug content.
5. More Economic and Ease of administration.
6. Tastelessness and Elegance.
7. Patient compliance.
8. They are in general the easiest and cheapest to package.
9. Optimal drug dissolution and hence, availability from the dosage form for absorption consistent with intended use.

1.5 Demerits:

1. Possess swallowing difficulty.
2. Onset of action is slow and depends on disintegration and dissolution. Some drugs resist compression, due to their amorphous nature or low-density.

1.6 Desired Criteria For Immediate Release Drug Delivery System

Immediate release dosage form should in the case of solid dosage it should dissolve or disintegrate in the stomach within a short period.

- ✓ In the case of liquid dosage form it should be compatible with taste masking.
- ✓ Be portable without fragility concern.
- ✓ Have a pleasing mouth feel.
- ✓ It should not leave minimal or no residue in the mouth after oral administration.
- ✓ Exhibit low sensitivity to environmental condition as humidity and temperature.
- ✓ Be manufactured using conventional processing and packaging equipment at low cost.
- ✓ Rapid dissolution and absorption of drug, which may produce rapid onset of action.

1.7 Other Excipients:

Excipients balance the properties of the actives in immediate release dosage forms. This demands a thorough understanding of the chemistry of these excipients to prevent interaction with the actives. Determining the cost of these ingredients is another issue that needs to be addressed by formulators. The role of excipients is important in the formulation of fast-melting tablets. These inactive food-grade ingredients, when incorporated in the formulation, impart the desired organoleptic properties and product efficacy. Excipients are general and can be used for a broad range of actives, except some actives that require masking agents.

1.7.1 Bulking Materials:

Bulking materials are significant in the formulation of fast melting tablets. The material contributes functions of a diluent, filler and cost reducer. Bulking agents improve the textural characteristics that in turn enhance the disintegration in the mouth, besides; adding bulk also reduces the concentration of the active in the composition. The recommended bulking agents for this delivery system should be more sugar-based such as mannitol, polydextrose, lactitol, DCL (direct compressible lactose) and starch hydrolysate for higher aqueous solubility and good sensory perception. Mannitol in particular has high aqueous solubility and good sensory perception. Bulking agents are added in the range of 10 percent to about 90 percent by weight of the final composition.

1.7.2 Emulsifying Agents:

Emulsifying agents are important excipients for formulating immediate release tablets they aid in rapid disintegration and drug release. In addition, incorporating emulsifying agents is useful in stabilizing the immiscible blends and enhancing bioavailability. A wide range of emulsifiers is recommended for fast-tablet formulation, including alkyl sulfates, propylene glycol esters, lecithin,

sucrose esters and others. These agents can be incorporated in the range of 0.05 percent to about 15 percent by weight of the final composition.

1.7.3 Lubricants:

Lubricants, though not essential excipients, can further assist in making these tablets more palatable after they disintegrate in the mouth. Lubricants remove grittiness and assist in the drug transport mechanism from the mouth down into the stomach.

1.7.4 Flavours and Sweeteners:

Flavours and taste-masking agents make the products more palatable and pleasing for patients. The addition of these ingredients assists in overcoming bitterness and undesirable tastes of some active ingredients. Both natural and synthetic flavours can be used to improve the organoleptic characteristic of fast-melting tablets. Formulators can choose from a wide range of sweeteners including sugar, dextrose and fructose, as well as non-nutritive sweeteners such as aspartame, sodium saccharin, sugar alcohols and sucralose. The addition of sweeteners contributes a pleasant taste as well as bulk to the composition.

1.7.5 Super Disintegrants:

A disintegrant is an excipient, which is added to a tablet or capsule blend to aid in the breakup of the compacted mass when it is put into a fluid environment.

Advantages:

1. Effective in lower concentrations
2. Less effect on compressibility and flowability
3. More effective intragranularly

1.7.5.1 Some super disintegrants are:

Sodium Starch Glycolate (Explotab, primogel) used in concentration of 2-8 % & optimum is 4%.

Mechanism of Action: Rapid and extensive swelling with minimal gelling. Microcrystalline cellulose (Synonym: Avicel, celex) used in concentration of 2-15% of tablet weight. And Water wicking.

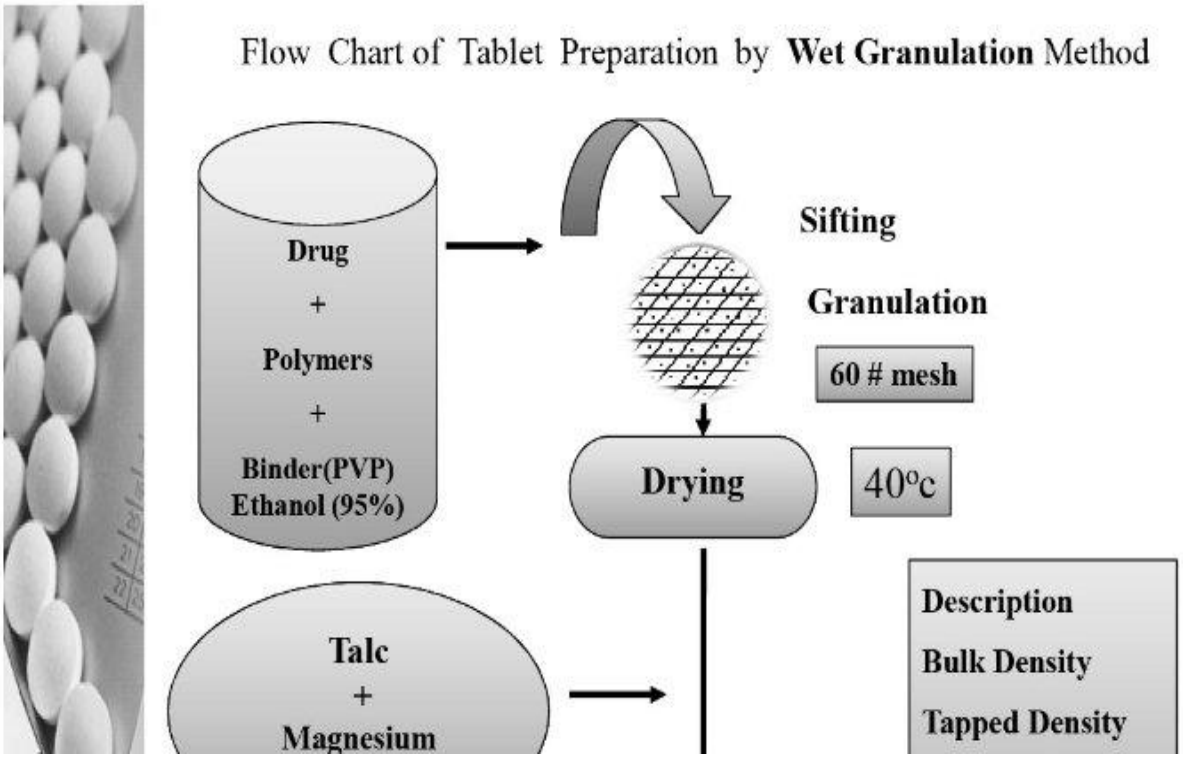


Figure 1.2 :Wet granulation

Dry granulation

In dry granulation process the powder mixture is compressed without the use of heat and solvent. The two basic procedures are to form a compact of material by compression and then to mill the compact to obtain granules. Two methods are used for dry granulation. The more widely used method is slugging, where the powder is precompressed and the resulting tablets or slugs are milled to yield granules. The other method is to precompress the powder with pressure rolls using a machine such as chilsonator.

Main Steps Involved in the Dry granulation method is

Milling of Drugs and Excipients
↓
Mixing of Milled powders
↓
Compression into large, hard tablets called slugs
↓
Screening of slugs
↓
Mixing with lubricant and disintegrating agent

Tablet Compression.

Direct compression method

The processing of drug with excipients can be achieved without any need of granulation and related unit operations. By simply mixing in a blender, formulation ingredients can be processed and compressed into tablets without any of the ingredients having to be changed. This procedure is called direct compression and it is used in the manufacture of tablets when formulation ingredients can flow uniformly into a die cavity.

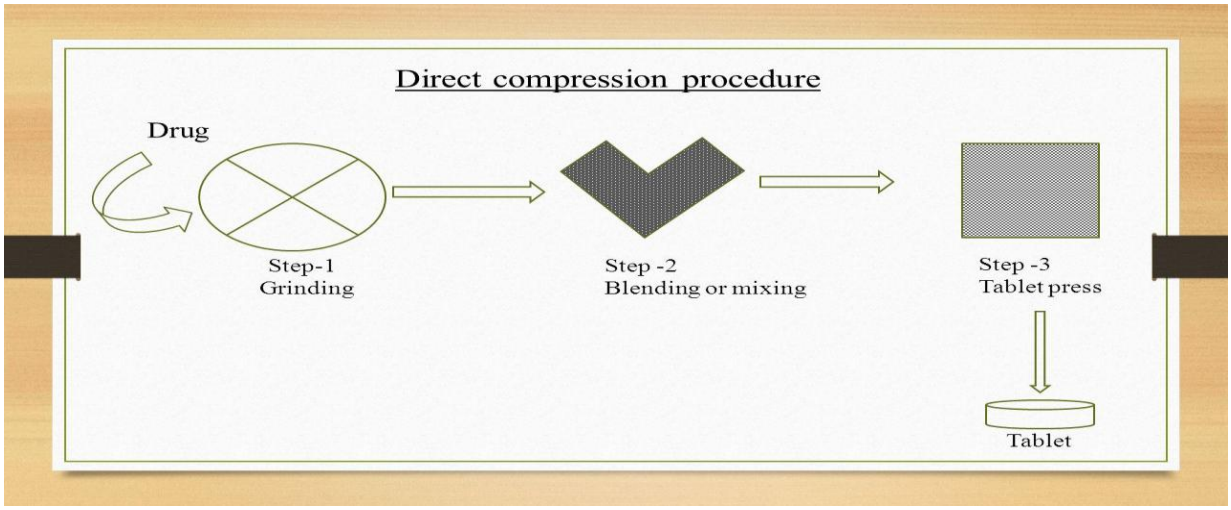


Figure 1.3 : Schematic representation of Direct compression method

II. LITERATURE REVIEW

1. A B Chinchawade et al., (2023):

Formulation and Evaluation of Immediate Release Tablet of Lercanidipine HCL. The aim of the present research work was to develop and formulate Immediate release tablet of Lercanidipine. Lercanidipine is an antihypertensive agent. Solid dispersion of Lercanidipine was prepared by spray drying method with different polymer for improvement of solubility resulting in improved bioavailabity. Immediate release tablet containing solid dispersion of Lercanidipine was compressed by direct compression method. The Immediate release properties of the tablets were achieved by the use of natural superdisintegrants for fast disintegration. The formulations were evaluated for various physical parameters, hardness, disintegration, dissolution studies and drug released mechanisms. Experimental batch number F6 formulation showed minimum disintegration time (30 sec) and maximum drug release duration of Lercanidipine spread over 1 hour.

2. Shweta Thakur et al., (2023):

Formulation and evaluation of immediate release tablet of Cisapride. The term “immediate release” pharmaceutical formulation includes any formulation in which the rate of release of drug from the

formulation or the absorption of drug, is neither appreciably, nor intentionally, retarded by galenic manipulations. These tablets which disintegrate rapidly and get dissolved to release the medicaments. It may be provided for by way of an appropriate pharmaceutically acceptable diluent or carrier, which diluent or carrier does not prolong, to an appreciable extent, the rate of drug release or absorption.

3. Bhupendra Singh et al., (2023):

Design, Formulation, and In-vitro Evaluation of Immediate Release Tablet of Etoricoxib. The current research aimed to formulate and evaluate the immediate-release tablet of etoricoxib. Etoricoxib belongs to BCS class II drugs; hence the solubility was enhanced using different techniques, thus achieving the dissolution of the drug. The formulation with maximum solubility enhancement was selected as the final formulation for the preparation of immediate-release tablets. These tablets were prepared using the wet granulation technique. Sodium starch glycolate was used as a super disintegrant, microcrystalline cellulose was used as a binder, and sodium bicarbonate was used as effervescent material for the preparation of an immediate-release tablet. Different trial batches were prepared and the formulations were optimized using design expert software. The optimized formulation was prepared and evaluated for different post-compression parameters. The disintegration time was found to be 2 minutes 16 seconds and the percent cumulative drug release was found to be 90.30%. The pharmacokinetic behavior of the drug was studied and first-order kinetics was found to be the best-fit model for immediate-release tablets. The accelerated stability study for the immediate-release tablet was carried out at 40°C ± 75% RH and different parameters were evaluated and were found within specified limits. Thus, immediate release tablets of etoricoxib were found to be a promising candidate for the treatment of acute pain or arthritis.

4. Muppavarapu Anusha et al., (2022):

Formulation and Evaluation of Immediate-Release Tablets of Edoxaban Tosylate. The immediate-release dosage form breaks down quickly and gets dissolved to release the medicaments. Immediate-release drug delivery is suitable for drugs having long biological half-life, high bioavailability, lower clearance, and lower elimination half-life. The basic design of the system consists of a rapid release core. The core tablets were prepared using rapid Mixer Granulation and Fluidized bed Granulation Technique. The Mixture was blended further with the addition of Crospovidone and Magnesium Stearate. Nine (F1-F9) formulations of the core were prepared using NF Pharma and HPC-L Nippon Soda as binders in different proportions (2, 3 & 4 %w/w) to study the effect of variable concentrations of these on the characteristics of the formulation. The core blend was evaluated for Flow properties, Hardness, Thickness, Friability, and in-vitro drug release. The drug (Edoxaban) is compatible with all excipients. All the parameters were in the optimum range. Among the Nine formulations F8 containing HPC Nippon Soda (2%) as a binder showed a better drug release of 100% over 60 minutes was selected. 400mg of resultant powder blend was manually compressed at a pressure of 100 tablets, with 10.60mm punch and die to obtain the core tablet. Among these, F8 was optimize based percent of drug release (99% of drug release in 60 minutes).

III. AIM AND OBJECTIVE

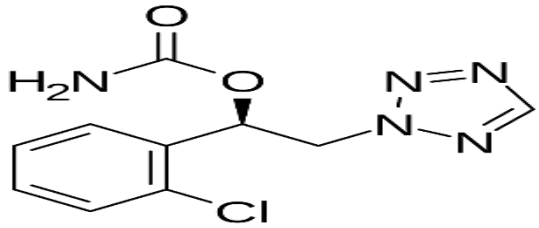
Aim: To formulate and evaluate immediate release tablets of Cenobamate in order to achieve rapid onset of action, enhanced bioavailability, and improved patient compliance in the management of seizures.

Objectives

1. To preformulate Cenobamate by studying its physicochemical properties and drug–excipient compatibility.
2. To develop immediate release tablets of Cenobamate using suitable excipients and formulation techniques.
3. To evaluate the prepared tablets for pre-compression parameters (flow properties, angle of repose, bulk density, etc.).
4. To carry out post-compression evaluation of tablets including weight variation, hardness, friability, thickness, disintegration time, drug content, and in vitro dissolution studies.
5. To compare the performance of different formulations and identify the optimized batch for immediate drug release.
6. To assess the optimized formulation against pharmacopoeial standards for quality and efficacy.

IV. DRUG PROFILE

- Drug: Cenobamate
- Synonym: XCOPRI
- Drug Category: Anticonvulsant
- Structure:



- Chemical Name / Nomenclature / IUPAC Name: 4-(2-Fluorophenyl)-2,3-dihydro-1H-pyrrolo[3,4-b]quinolin-1-one
- Molecular Formula: $C_{14}H_{12}FN_3O$
- Molecular Weight: 257.27 gm/mole

4.1 PHYSICOCHEMICAL PROPERTIES:

Description (Physical State): White to off-white crystalline powder

Solubility: Sparingly soluble in water, soluble in ethanol

Stability: Stable under normal conditions, sensitive to light and moisture

Storage Conditions: Store in a tightly closed container at room temperature (20–25°C), away from light and moisture

Dosage: 100 mg to 200 mg once daily (starting dose is typically low and gradually increased)

Melting Point: Approximately 135°C

pKa (strongest acidic): Not readily available in standard databases

Log P: 3.4 (indicating moderate lipophilicity)

4.2 PHARMACOKINETIC PROPERTIES:

Bioavailability: Approximately 90%

Half-life: 50–60 hours

Absorption: Well absorbed after oral administration, peak plasma concentration typically occurs within 4–5 hours

Volume of Distribution: 0.9 L/kg

Protein Binding: 70%

Metabolism: Metabolized primarily in the liver by CYP3A4

Metabolites: Inactive metabolites

Time of Peak Action: 4–5 hours after oral administration

Excretion: Excreted primarily in the urine (approximately 80%), with a small amount in the feaces

4.3 ADVERSE EFFECTS/SIDE EFFECTS:

Common: Somnolence, dizziness, headache, fatigue, nausea

Serious: QT prolongation, suicidal ideation, severe allergic reactions (e.g., angioedema, anaphylaxis)

Rare but Severe: Multiorgan hypersensitivity reactions, liver dysfunction, serious dermatologic reactions

4.4 PHARMACODYNAMICS:

Mechanism of Action: Cenobamate works by reducing neuronal excitability through dual mechanisms. It inhibits voltage-gated sodium channels, stabilizing hyperactive neurons, and enhances the inhibitory action of GABA (gamma-aminobutyric acid) at GABA-A receptors. This combination makes it effective for controlling seizures in patients with epilepsy.

Therapeutic Efficacy/Indications:

- Approved for the treatment of focal onset seizures in patients with epilepsy, both as monotherapy and adjunctive therapy.
- Can be used in adults who have not responded adequately to other antiepileptic drugs (AEDs).

Adverse Reactions: Common side effects include drowsiness, dizziness, and headache. More serious risks involve prolonged QT interval, suicidal thoughts, and severe skin reactions.

Contraindications:

- Hypersensitivity to cenobamate or any of its components
- Concomitant use with strong CYP3A4 inhibitors (e.g., ketoconazole) is contraindicated due to increased risk of adverse effects.
- Caution is required in patients with a history of cardiac arrhythmias or QT prolongation.

4.5 INTERACTIONS:

4.5.1 Drug Interactions:

- CYP3A4 Inhibitors (e.g., ketoconazole, itraconazole, clarithromycin): Concomitant use may increase cenobamate plasma concentrations, requiring dose adjustment.
- CYP3A4 Inducers (e.g., carbamazepine, rifampin): May decrease cenobamate plasma concentrations, potentially reducing efficacy.
- Other Antiepileptic Drugs (AEDs): Careful monitoring is required when used with other

AEDs to prevent additive CNS depressant effects.

- Oral Contraceptives: Cenobamate may reduce the effectiveness of oral contraceptives by increasing their metabolism, necessitating alternative contraception.
- Alcohol: Should be avoided as it can increase the sedative effect and exacerbate CNS depression.

V. EXCIPIENTS PROFILE

5.1 CROSPOVIDONE

Nonproprietary Names:

BP: Crospovidone, PhEur: Crospovidone, USP-NF: Crospovidone

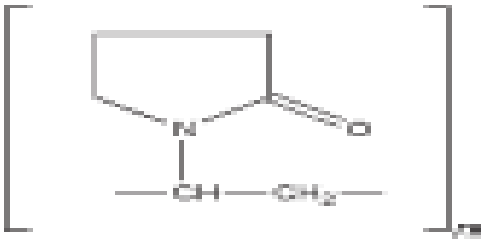
Synonyms:

Crospovidonum; Crospopharm; crosslinked povidone; E1202; Kollidon CL; Kollidon CL-M; Polyplasdone XL.

Chemical Name and CAS Registry Number:

1-Ethenyl-2-pyrrolidinone homopolymer [9003-39-8]

Structural formula:



Functional Category:

Tablet disintegrant.

Applications in Pharmaceutical Formulation or Technology:

Crospovidone is a water-insoluble tablet disintegrant and dissolution agent used at 2–5% concentration in tablets prepared by direct compression or wet- and dry-granulation methods. It rapidly exhibits high capillary activity and pronounced hydration capacity, with little tendency to form gels. Studies suggest that the particle size of crospovidone strongly influences disintegration of analgesic tablets. Larger particles provide a faster disintegration than smaller particles. Crospovidone can also be used as a solubility enhancer. With the technique of co-evaporation, crospovidone can be used to enhance the solubility of poorly soluble drugs. The drug is adsorbed on to crospovidone in the presence of a suitable solvent and the solvent is then evaporated. This technique results in faster dissolution rate.

Description:

Crospovidone is a white to creamy-white, finely divided, free flowing, practically tasteless, odorless or nearly odorless, hygroscopic powder.

Stability and Storage Conditions:

Since crospovidone is hygroscopic, it should be stored in an airtight container in a cool, dry place.

Incompatibilities:

Crospovidone is compatible with most organic and inorganic pharmaceutical ingredients. When exposed to a high water level, crospovidone may form molecular adducts with some materials.

Safety:

Crospovidone is used in oral pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material. Short-term animal toxicity studies have shown no adverse effects associated with crospovidone. However, owing to the lack of available data, an acceptable daily intake in humans has not been specified by the WHO.

LD50 (mouse, IP): 12 gm/kg

Handling Precautions:

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection, gloves, and a dust mask are recommended.

5.2 CROSS CARMELLOSE SODIUM

Nonproprietary Name:

BP: Croscarmellose Sodium, JP: Croscarmellose Sodium, PhEur: Croscarmellose Sodium

USP-NF: Croscarmellose Sodium

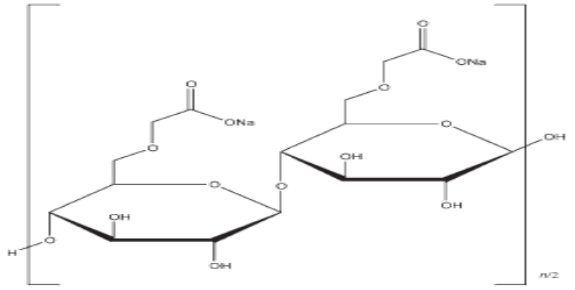
Synonyms:

Ac-Di-Sol; carmellosum natricum conexum; crosslinked carboxymethylcellulose sodium; Explocel; modified cellulose gum; Nymcel ZSX; Pharmacel XL; Primellose; Solutab; Vivasol.

Chemical Name and CAS Registry Number:

Cellulose, carboxymethyl ether, sodium salt, crosslinked [74811-65-7]

Structural Formula:



Functional Category: Tablet and capsule disintegrant.

Applications in Pharmaceutical Formulation or Technology:

Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for capsules, tablets and granules. In tablet formulations, croscarmellose sodium may be used in both direct-compression and wet-granulation processes. When used in wet granulations, the croscarmellose sodium should be added in both the wet and dry stages of the process (intra and extra-granularly) so that the wicking and swelling ability of the disintegrant is best utilized. Croscarmellose sodium at concentrations up to 5% w/w may be used as a tablet disintegrant, although normally 2% w/w is used in tablets prepared by direct compression and 3% w/w in tablets prepared by a wet-granulation process.

Use Concentration (%)

Disintegrant in capsules 10–25

Disintegrant in tablets 0.5–5

Description:

Croscarmellose sodium occurs as an odorless, white or grayish white powder.

Stability and Storage Conditions:

Croscarmellose sodium is a stable though hygroscopic material. A model tablet formulation prepared by direct compression, with croscarmellose sodium as a disintegrant, showed no significant difference in drug dissolution after storage at 30^0C for 14 months. Croscarmellose sodium should be stored in a well-closed container in a cool, dry place.

Incompatibilities:

The efficacy of disintegrants, such as croscarmellose sodium, may be slightly reduced in tablet formulations prepared by either the wet-granulation or direct-compression process that contain hygroscopic excipients such as sorbitol. Croscarmellose sodium is not compatible with strong acids or with soluble salts of iron and some other metals such as aluminum, mercury, and zinc.

Safety:

Croscarmellose sodium is mainly used as a disintegrant in oral pharmaceutical formulations and is generally regarded as an essentially nontoxic and nonirritant material. However, oral consumption of large amounts of croscarmellose sodium may have a laxative effect, although the quantities used in solid dosage formulations are unlikely to cause such problems. In the UK, croscarmellose sodium is accepted for use in dietary supplements. The WHO has not specified an acceptable daily intake for the related substance carboxymethylcellulose sodium, used as a food additive, since the levels necessary to achieve a desired effect were not considered sufficient to be a hazard to health.

Handling Precautions:

Observe normal precautions appropriate to the circumstances and quantity of material handled. Croscarmellose sodium may be irritant to the eyes; eye protection is recommended.

5.3 SODIUM STARCH GLYCOLATE

Nonproprietary Names :

BP: Sodium Starch Glycolate,

PhEur: Sodium Starch Glycolate,

USP-NF: Sodium Starch Glycolate

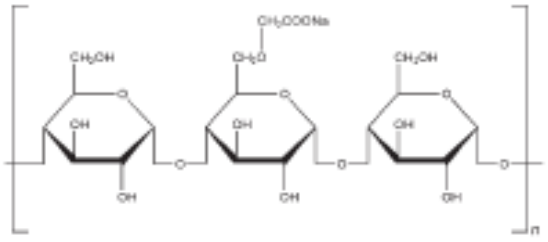
Synonyms:

Carboxymethyl starch, sodium salt; carboxymethylamylum natricum; Explosol; Explotab; Glycolys; Primojel; starch carboxymethyl ether, sodium salt; Tablo; Vivastar .

Chemical Name and CAS Registry Number:

Sodium carboxymethyl starch [9063-38-1]

Structural Formula:



Functional Category :

Tablet and capsule disintegrant.

Applications in Pharmaceutical Formulation or Technology:

Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations. It is commonly used in tablets prepared by either direct-compression or wet-

granulation processes. The usual concentration employed in a formulation is between 2% and 8%, with the optimum concentration about 4%, although in many cases 2% is sufficient. Disintegration occurs by rapid uptake of water followed by rapid and enormous swelling. Although the effectiveness of many disintegrants is affected by the presence of hydrophobic excipients such as lubricants, the disintegrant efficiency of sodium starch glycolate is unimpaired. Increasing the tablet compression pressure also appears to have no effect on disintegration time. Sodium starch glycolate has also been investigated for use as a suspending vehicle.

Description:

Sodium starch glycolate is a white or almost white free-flowing very hygroscopic powder. The PhEur 6.0 states that when examined under a microscope it is seen to consist of: granules, irregularly shaped, ovoid or pear-shaped, 30–100 mm in size, or rounded, 10–35 mm in size; compound granules consisting of 2–4 component occur occasionally; the granules have an eccentric hilum and clearly visible concentric striations. Between crossed nicol prisms, the granules show a distinct black cross intersecting at the hilum; small crystals are visible at the surface of the granules. The granules show considerable swelling in contact with water.

Stability and Storage Conditions:

Tablets prepared with sodium starch glycolate have good storage properties. Sodium starch glycolate is stable although very hygroscopic, and should be stored in a well-closed container in order to protect it from wide variations of humidity and temperature, which may cause caking. The physical properties of sodium starch glycolate remain unchanged for up to 3 years if it is stored at moderate temperatures and humidity.

Incompatibilities:

Sodium starch glycolate is incompatible with ascorbic acid.

Safety:

Sodium starch glycolate is widely used in oral pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material. However, oral ingestion of large quantities may be harmful.

Handling Precautions:

Observe normal precautions appropriate to the circumstances and quantity of material handled. Sodium starch glycolate may be irritant to the eyes; eye protection and gloves are recommended. A dus mask or respirator is recommended for processes that generate a large quantity of dust.

5.4 MICROCRYSTALLINE CELLULOSE

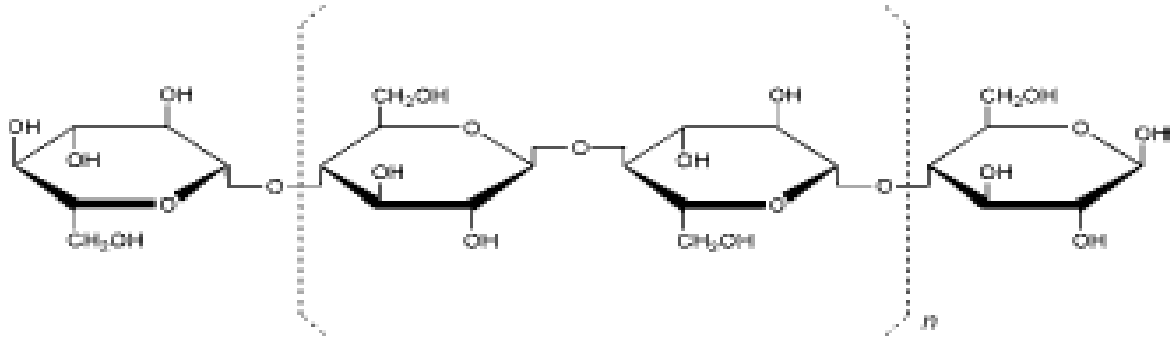
Synonyms Avicel PH; Celex; cellulose gel Celphere. Celous KG Crystalline cellulose E460, Emocel, thispheres.

Empirical Formula $(C_6H_{10}O_5)n$ where n ≈ 220.

Chemical Name Cellulose

Molecular Weight ≈ 36000

Structural formula.



Functional Category: Adsorbent, suspending agent, tablet and capsule diluents tablet disintegrant

Applications: Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluents in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes. In addition to its uses as a binder/diluents microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting Microcrystalline cellulose is also used in cosmetics and food products.

Table 7.2: Use of microcrystalline cellulose.

Use	Concentration (%)
Adsorbent	20–90
Antiadherent	5–20
Capsule binder/diluent	20–90
Tablet disintegrant	5–15
Tablet binder/diluent	20–90

Description: Microcrystalline cellulose is purified partially depolymerize cellulose that occurs as a white, odorless, tasteless and crystalline powder composed of porous particles. It is commercially available in different particle size, moisture grades that have different properties and application.

Angle of repose (θ)	34.4º
Density (bulk)	0.337g/cm^3 for Avicel PH200 0.32g/cm^3 for Avicel PH101
Density (tapped)	0.478g/cm^3 for Avicel 200 0.45g/cm^3 for Avicel PH101
Density (true)	1.512-1.668g/cm^3
Flowability	1.41g/s
Melting point	260-270ºC
Particle size distribution	Typical mean particle size is 20-200 µm
Moisture content	Typically less than 5% w/w it is hygroscopi.
Solubility	Typically less than 5% w/w it is hygroscopi
Moisture content	Slightly soluble in 5% w/v sodium hydroxide solution practically insoluble in water dilute acids.
Stability	Microcrystalline cellulose is a stable though hygroscopic material
Storage condition	The bulk material should be stored in a well closed container in a cool dry place
Safety :	It is widely used in oral pharmaceutical formulation is generally regarded as a relatively nontoxic and nonirritant material. Deliberate abuse of formulations contacting cellulose either by inhalation or by injection, has resulted in the formation of cellulose granulomas.

5.5 ASPARTAME

Nonproprietary Names :

- BP: Aspartame
- PhEur: Aspartamum
- USPNF: Aspartame

Synonyms :

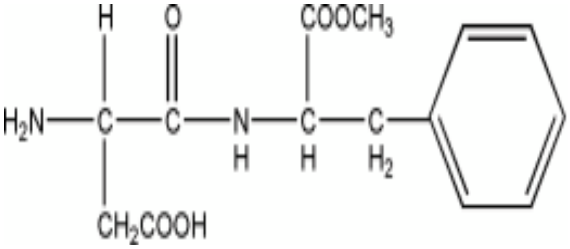
3-Amino-N-(α-carboxyphenethyl)succinamic acid N-methyl ester; 3-amino-N-(α-methoxycarbonylphenethyl)succinamic acid; APM; aspartyl phenylamine methyl ester; methyl N-α-L-aspartyl-L-phenylalaninate;

Chemical Name and CAS Registry Number: N-α-L-Aspartyl-L-phenylalanine 1-methyl ester [22839-47-0]

Empirical Formula and Molecular Weight: $C_{14}H_{18}N_2O_5$ and 294.31

Description: Aspartame occurs as an off white, almost odorless crystalline powder with an intensely sweet taste.

Structural Formula :



Functional Category Sweetening agent.

Applications in Pharmaceutical Formulation or Technology : Aspartame is used as an intense sweetening agent in beverage products, food products, and table-top sweeteners, and in pharmaceutical preparations including tablets,powder mixes, and vitamin preparations. It enhances

flavor systems and can be used to mask some unpleasant taste characteristics; the approximate sweetening power is 180–200 times that of sucrose. Unlike some other intense sweeteners, aspartame is metabolized in the body and consequently has some nutritive value: 1 g provides approximately 17 kJ (4 kcal). However, in practice, the small quantity of aspartame consumed provides a minimal nutritive effect. Therapeutically, aspartame has also been used in the treatment of sickle cell anemia

5.6 MG STEARATE

Synonyms Magnesium octadecanoate; octadecanoic acid, magnesium salt; stearic acid, magnesium salt.

Molecular weight 591.34.

Structural formula $[CH_3(CH_2)_{16}COO]_2Mg$

Functional category: Tablet and capsule lubricant

Applications in pharmaceutical formulation technology It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25 % and 5.0 % w/w.

Description Magnesium stearate is a fine, white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to touch and readily adheres to the skin.

Crystalline forms High purity magnesium stearate has been isolated as a trihydrate, dihydrate and an anhydrate.

Flowability Poorly flowing, cohesive powder.

Melting range 117-150° C (commercial samples) 126-130° C (high purity magnesium stearate).

Solubility Practically insoluble in ethanol, ethanol (95 %), ether and water; slightly soluble in warm benzene and warm ethanol (95 %).

Specific surface area 1.6-14.8 m^2/g

Stability and Storage Conditions Magnesium stearate is stable and should be stored in a well-closed container in a cool and dry place.

Incompatibilities: Incompatible with strong acids, alkalis and iron salts strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins and most alkaloid salts.

Method of manufacture: Magnesium stearate is prepared either by the interaction of aqueous solutions of magnesium Chloride with sodium stearate or by the interaction of magnesium oxide, hydroxide or carbonate with stearic acid at elevated temperatures.

5.7 TALC

Synonym: Altalc; E553b; hydrous magnesium calcium silicate; hydrous magnesium silicate; Luzenac pharma; magnesium hydrogen metasillicate; Magsil Osmanthus: Madsil star; powdered talc; purified French chalk ; Purtalc;soapstones;

Functional category: Anticaking agent; Tablet and Capsule diluents; Tablet and capsule lubricant.

Application in pharmaceutical formulations: Used in oral solid dosage formulation as a lubricant and glidant (1-10%) Dissolution retardant in the development of controlled release products. Used as dusting powder (90.0-99.0), Lubricant properties in cosmetics and food properties, Talc is widely used in oral solid dosage formulations as lubricant and diluents.

VI. METHODOLOGY

6.1 Buffer Preparation:

Preparation of 0.2M Potassium dihydrogen orthophosphate solution: Accurately weighed 27.218 gm of monobasic potassium dihydrogen orthophosphate was dissolved in 1000mL of distilled water and mixed.

Preparation of 0.2M sodium hydroxide solution: Accurately weighed 8 gm sodium hydroxide pellets were dissolved 1000ml of distilled water and mixed.

Preparation of pH 6.8 Phosphate buffer: Accurately measured 250ml of 0.2M potassium Dihydrogen ortho phosphate and 112.5 ml 0.2M NaOH was taken into the 1000ml volumetric flask. Volume was made up to 1000ml with distilled water.

6.2 Analytical method development for Cenobamate:

a) Determination of absorption maxima

A spectrum of the working standards was obtained by scanning from 200-400nm against the reagent blank to fix absorption maxima. The λ_{max} was found to be 254 nm. Hence all further investigation was carried out at the same wavelength.

b) Preparation of Standard graph in pH 6.8 phosphate buffer

100 mg of Cenobamate was dissolved in 100ml of Phosphate buffer of pH 6.8., form primary stock 10ml was transferred to another volumetric flask made up to 100ml with Phosphate buffer of pH 6.8, from this secondary stock was taken separately and made up to 10 ml with Phosphate buffer of pH 6.8, to produce 10, 20, 30, 40 and 50µg/ml respectively. The

absorbance was measured at 254 nm by using a UV spectrophotometer.

6.3 Formulation Development:

Drug and different concentrations for super Disintegrates and required ingredients were accurately weighed and passed through a 40-mesh screen to get uniform size particles and mixed in a glass mortar for 15 minutes. The obtained blend was lubricated with Magnesium stearate and glidant (Talc) was added and mixing was continued for further 5 minutes. The resultant mixture was directly compressed into tablets by using punch of rotary tablet compression machine. Compression force was kept constant for all formulations.

6.4 Pre formulation Studies

6.4.1 Pre compression parameters:

Measurement of Micromeritic Properties of Powders

1. Angle of repose

The angle of repose of API powder is determined by the funnel method. The accurately weight powder blend are taken in the funnel. The height of the funnel is adjusted in way that, the tip of the funnel just touched the apex of the powder blend. The powder blend is allowed to flow through the funnel freely on the surface. The diameter of the powder cone is measured and angle of repose is calculated using the following equation.

$\tan \theta = h/r$ (1)

where, h and r are the height and radius of the powder con

Flow Property	Angle of Repose (^{0})
Excellent	25-30
Good	31-35
Fair- aid not needed	36-40
Passable-may hang up	41-45
Poor-must agitate, Vibrate	46-55
Very Poor	56-65
Very, very Poor	>66

Table 6.2: Flow Properties and Corresponding Angle of Repose

2. Bulk density

The powder sample under test is screened through sieve No.18 and the sample equivalent to 25 gm is weighed and filled in a 100 ml graduated cylinder and the power is leveled and the unsettled volume, V_o is noted. The bulk density is calculated in g/cm^3 by the formula.

Bulk density = M/V_0 (2)

M= Powder mass

V_0= apparent unstrirred volume

3. Tapped density

The powder sample under test is screened through sieve No.18 and the weight of the sample equivalent to 25 gm filled in 100 ml granulated cylinder. The mechanical tapping of cylinder is carried out using tapped density tester at a nominal rate for 500 times initially and the tapped volume V_0 is noted. Tappings are preceded further for an additional tapping 750 times and tapped volume, Vb is noted. The difference between two tapping volume is less than 2%, V_b is considered as a tapped volume V_f . the tapped density is calculated in g/cm^3 by the formula.

Tapped density=M/V_f (3)

M= weight of sample power taken

V_f= tapped volume

4. Compressibility Index

The Compressibility Index of the power blend is determined by Carr's compressibility index to know the flow character of a powder. The formula for Carr's Index is a below:

Carr's Index (%)=[(TD-BD)/TD]x100 (4)

5. Hauser's ratio

The Hauser's ratio is a number that is correlated to the flowability of a powder or granular material. The ratio of tapped density to bulk density of the powders is called the Hauser's ratio. It is calculated by the following equation.

$H=\rho T / \rho B$ (5)

Where ρT= tapped density, ρB = bulk density

Table 6.3: Scale of Flowability

Compressibility index (%)	Flow character	Hausner Ratio
≤ 10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very Poor	1.46-1.59
> 38	Very, very Poor	> 1.60

6.4.2 Post compression parameters:

a) Thickness

The thickness of tablets was determined by using Digital micrometer. Ten individual tablets from each batch were used and the results averaged.

b) Weight variation

Twenty tablets randomly selected from each batch and individually. Weighed the average weight and standard deviation three batches were calculated. It passes the test weight variation test if not more than two of the individual tablets weights deviate from the average weight by more than the allowed percentage deviation and more deviate by more than twice the percentage shown. It was calculated on an electronic weighing balance.

c) Friability

The friability values of the tablets were determined using a Roche-type friabilator. Accurately weighed six tablets were placed in Roche friabilator and rotated at 25rpm for 4 min.

Percentage friability was calculated using the following equation.

$$\text{Friability} = ([w_0\text{-}w] / w_0) \times 100$$

d) Assay

The content of drug was carried out by five randomly selected tablets of each formulation. The five tablets were grinded in mortar to get powder; this powder was dissolved in pH 6.8 phosphate buffer by sonication for 30 min and filtered through filter paper. The drug content was analyzed spectrophotometrically at 254 nm using UV spectrophotometer. Each measurement was carried out in triplicate and the average drug content was calculated.

e) Disintegration test

Six tablets were taken randomly from each batch and placed in USP disintegration apparatus baskets. Apparatus was run for 10 minutes and the basket was lift from the fluid, observe whether all of the tablets have disintegrated.

f) Dissolution test of Cenobamate tablets

Drug release from Cenobamate tablets was determined by using dissolution test United States Pharmacopoeia (USP) 24 type II (paddle). The parameters used for performing the dissolution were pH 6.8 phosphate buffer as the dissolution medium of quantity 500ml. the whole study is being carried out at a temperature of 37^0C and at speed of 50 rpm.

5 ml aliquots of dissolution media were withdrawn each time at suitable time intervals (5, 10, 15, 20, 25, 30 and 45minutes) and replaced with fresh medium. After withdrawing, samples were filtered and analyzed after appropriate dilution by UV Spectrophotometer. The concentration was calculated using standard calibration curve.

6.5 Drug-Excipients compatibility studies:

Drug excipients compatibility studies were carried out by mixing the drug with various excipients in different proportions (in 1:1 ratio were prepared to have maximum likelihood interaction between them)

was placed in a vial, and closed with rubber stopper and sealed properly.

VII. RESULTS AND DISCUSSION

7.1 Determination of λ_{max} :

The prepared stock solution was scanned between 200-400 nm to determine the absorption maxima. It was found to be 254nm.

7.2 Calibration curve of Cenobamate:

The standard curve of Cenobamate was obtained and good correlation was obtained with R^2 value of 0.999, the medium selected was pH 6.8 phosphate buffer.

Table 8.1: Standard graph values of Cenobamate at 254 nm in pH 6.8 phosphate buffer

Concentrations (µg/ml)	Absorbance
0	0
10	0.148
20	0.292
30	0.429
40	0.582
50	0.718

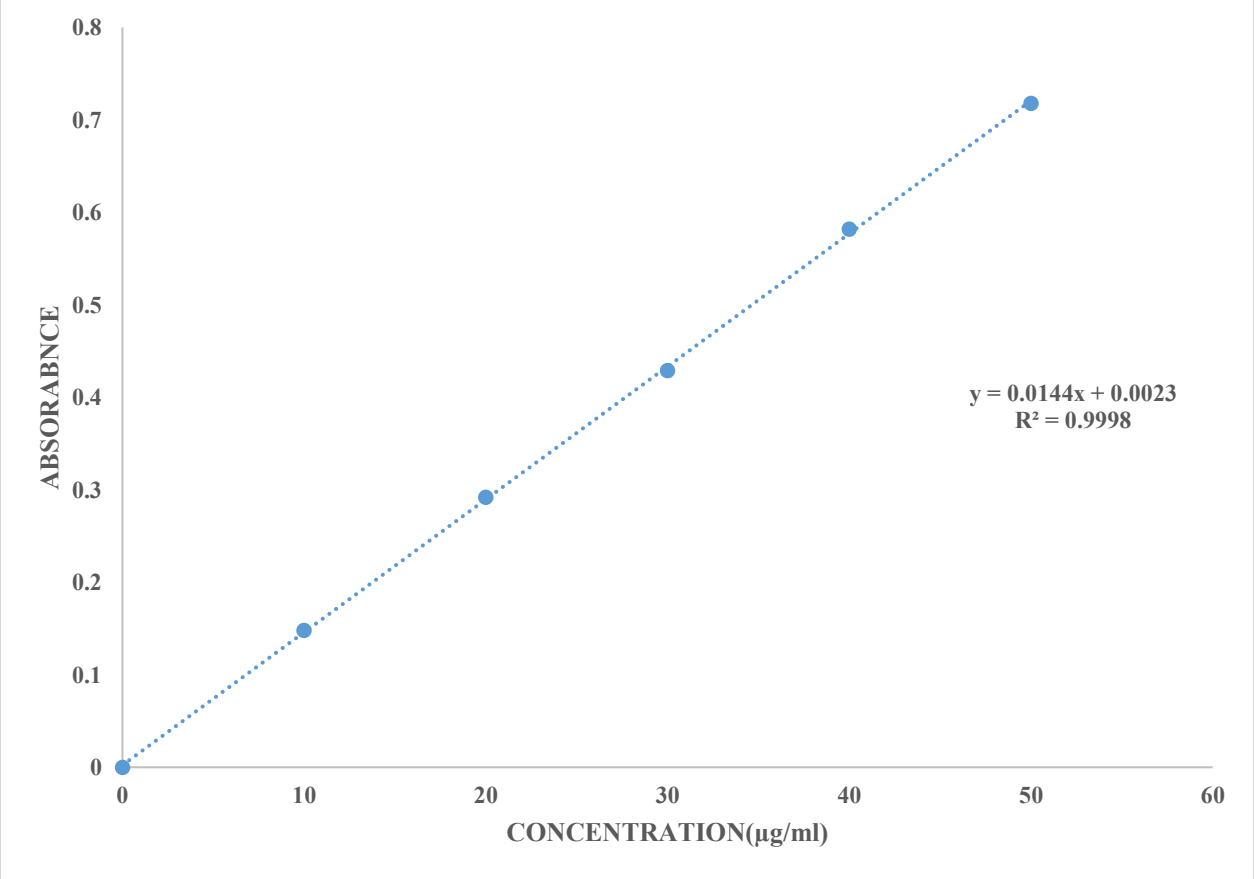


Fig 7.1: Standard curve of Cenobamate

7.3 Evaluation:

7.3.1 Characterization of precompression blend:

The precompression blend of Cenobamate was characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio. Angle of repose was less than 27.8º, Carr's index values were less than 13.9 for the precompression blend of all the batches indicating good to fair flowability and compressibility. Hausner's ratio was less than 1.16 for all batches indicating good flow properties

Table 7.2: Physical properties of precompression blend

Formulation code	Angle of repose (Ɵ)	Bulk density (gm/cm^3	Tapped density(gm/cm^3)	Carr's index (%)	Hausner's ratio
F1	25.23	0.515	0.598	13.88	1.161
F2	23.25	0.525	0.61	13.934	1.162
F3	24.62	0.535	0.609	12.151	1.138
F4	24.56	0.512	0.587	12.777	1.146
F5	25.72	0.499	0.574	13.066	1.15
F6	24.3	0.512	0.582	12.027	1.137
F7	27.8	0.502	0.572	12.238	1.139
F8	25.54	0.518	0.586	11.604	1.131
F9	26.32	0.486	0.564	13.83	1.16

All the values represent n=3

7.4 Evaluation of tablets:

a) Physical evaluation of Cenobamate immediate release tablets:

The results of the weight variation, hardness, thickness, friability and drug content of tablets are given in table 8.3. All the tablets of different batches complied with the official requirement of weight variation as their weight variation passes the limit. The hardness of the tablets ranged from 2.9 – 3.7 kg/cm^2 and the friability values were < than 0.68 % indicating that the tablets were compact and hard. The thickness of the tablets ranged from 2.12 - 2.91 mm. All the formulations satisfied the content of the drug as they contained 98.15-100.12 % of Cenobamate and good uniformity in drug content was observed. Thus, all physical attributes of the prepared tablets were found to be practically within control limits.

Table 7.3: Physical evaluation of Cenobamate

Formulation code	Weight variation (mg)	Thickness (cm)	Hardness (Kg/cm^2)	Friability (%)	Content Uniformity (%)	Disintegration Time (Sec)
F1	199.52	2.26	3.3	0.66	98.64	63
F2	200.21	2.70	3.7	0.53	99.08	54
F3	199.12	2.15	3.0	0.44	100.12	41
F4	198.86	2.55	2.9	0.41	99.31	47
F5	199.72	2.88	3.6	0.36	98.54	36
F6	200.25	2.91	3.7	0.25	99.22	29
F7	198.47	2.12	2.9	0.31	98.94	52
F8	201.23	2.71	3.2	0.26	99.20	47
F9	196.61	2.84	3.4	0.28	98.16	33

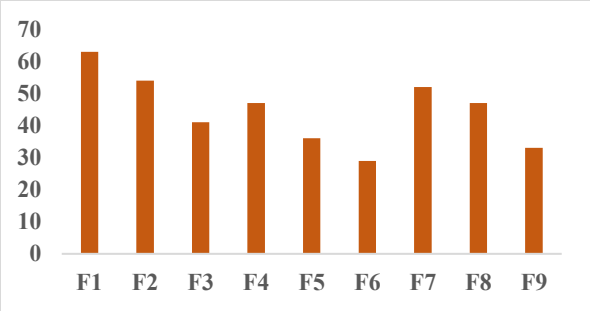


Figure 7.2: Disintegration Test (Sec)

b) In vitro release studies:The drug release rate from tablets was studied using the USP type II dissolution test apparatus. The dissolution medium was 500 ml of pH 6.8 phosphate buffer at 50 rpm at a temperature of 37±0.5 ˚C. Samples of 5 ml were collected at different time intervals up to 1 hr and has analyzed after appropriate dilution by using UV spectrophotometer at 254 nm.

Table 7.4: In vitro dissolution data for formulation F1-F9

TIME (MIN)	% OF DRUG RELEASE								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	26.01	29.11	33.09	29.83	34.19	43.41	18.61	29.60	33.78
10	31.89	35.33	41.26	38.36	47.37	55.95	26.46	41.15	47.52
15	38.34	47.82	52.64	47.02	56.61	61.38	43.23	47.01	57.32
20	43.65	54.91	58.35	56.24	65.94	77.92	52.19	58.62	69.01
25	57.21	66.12	71.51	62.06	77.22	84.06	64.92	75.41	82.98
30	67.97	78.74	74.78	79.98	82.41	93.41	75.27	82.28	89.81
45	83.64	89.03	85.17	88.51	95.86	99.37	96.11	91.31	93.35

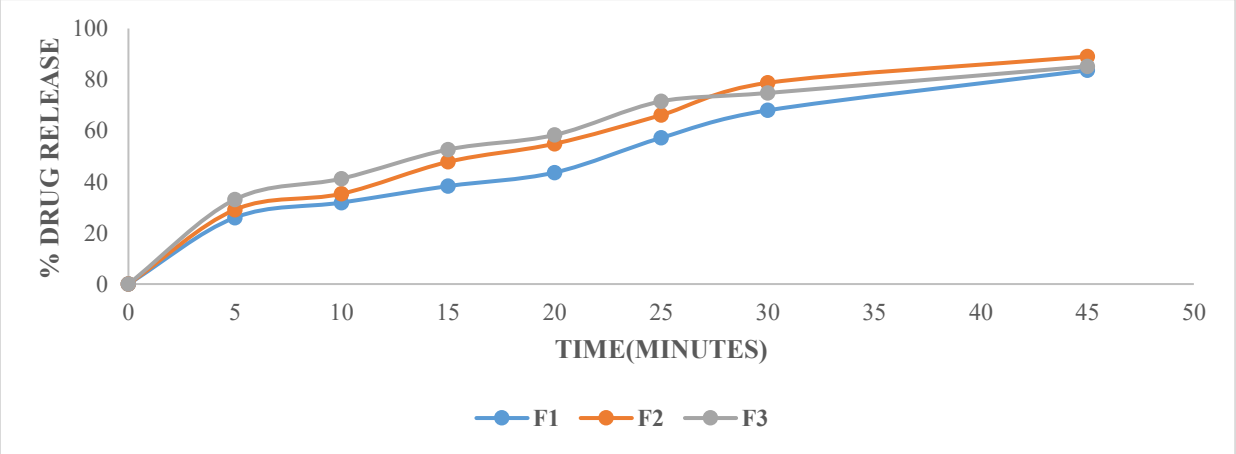


Fig 8.3: In vitro dissolution data for formulation F1-F3

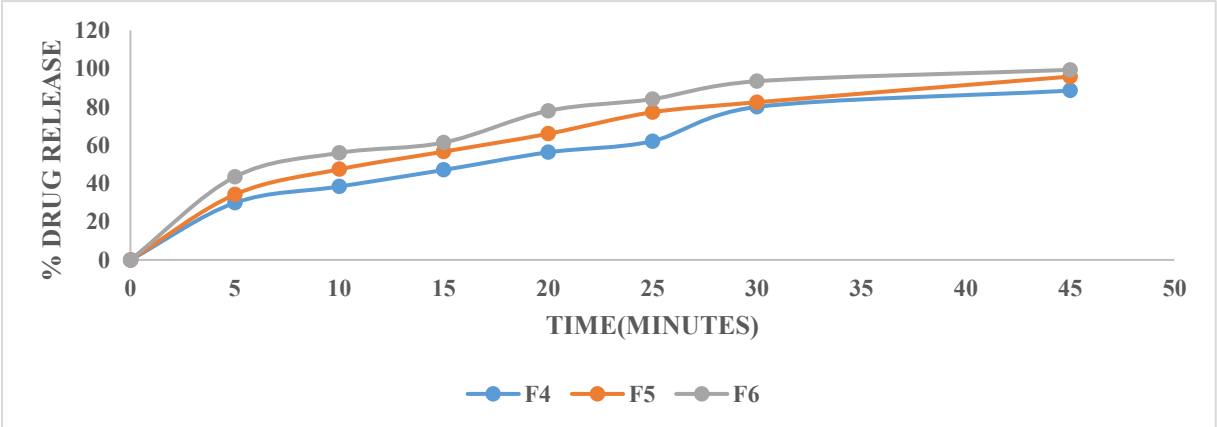


Fig 7.4: In vitro dissolution data for formulations F4-F6

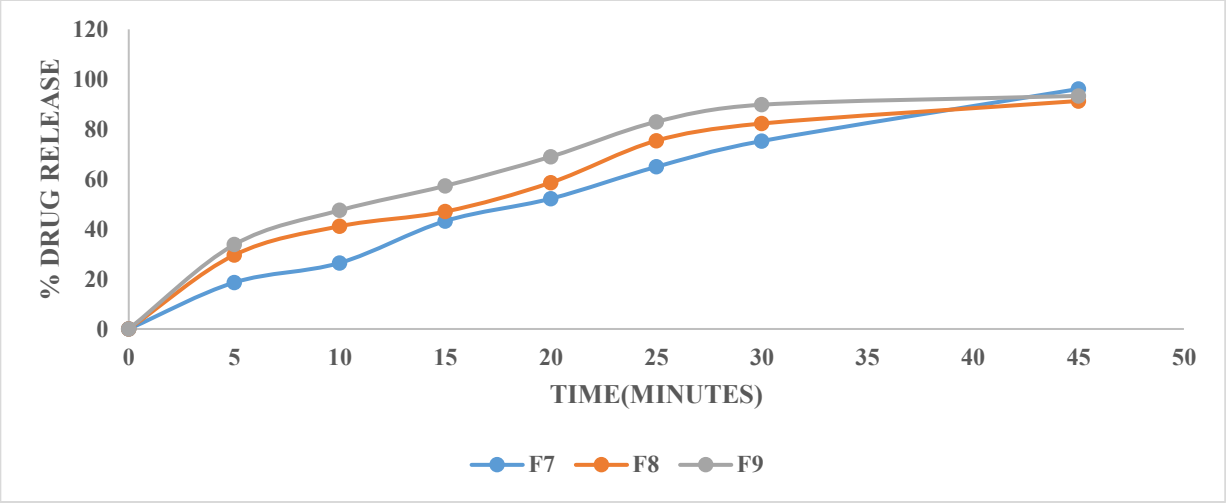


Fig 7.5: In vitro dissolution data for formulations F7-F9

From the table it was evident that the formulation prepared with Crospovidone were showed good drug release i.e., F2 formulation (89.03%) in higher concentration of blend i.e. 50 mg. Formulations prepared with Croscarmellose sodium showed good drug release i.e., 99.37 % (F6 formulation) in 75 mg concentration. When increase in the concentration of Cros carmellose sodium drug release increased. Formulations prepared with Sodium starch glycolate showed maximum drug release i.e., 96.11% (F7formulation) at 45 min in 25 mg of blend.

Among all formulations F6 considered as optimized formulation which showed maximum drug release at 45 min i.e., 99.37 %. Cros carmellose sodium showed good release when compared to Crospovidone and Sodium starch glycolate. Finally concluded that F6 formulation contains Cros carmellose sodium was optimized formulation.

c) Drug-Excipient compatibility studies by FTIR studies:

Cenobamate was mixed with various proportions of excipients showed no colour change at the end of two months, providing no drug –excipient interactions.

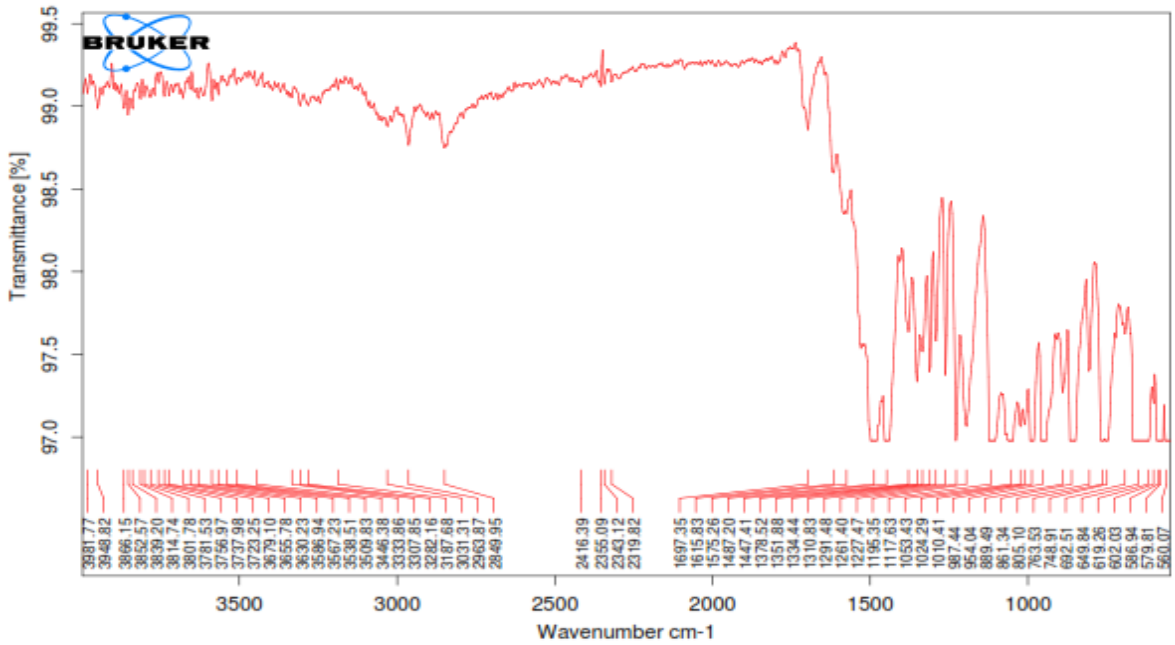


Fig 7.6: FTIR spectra of pure drug

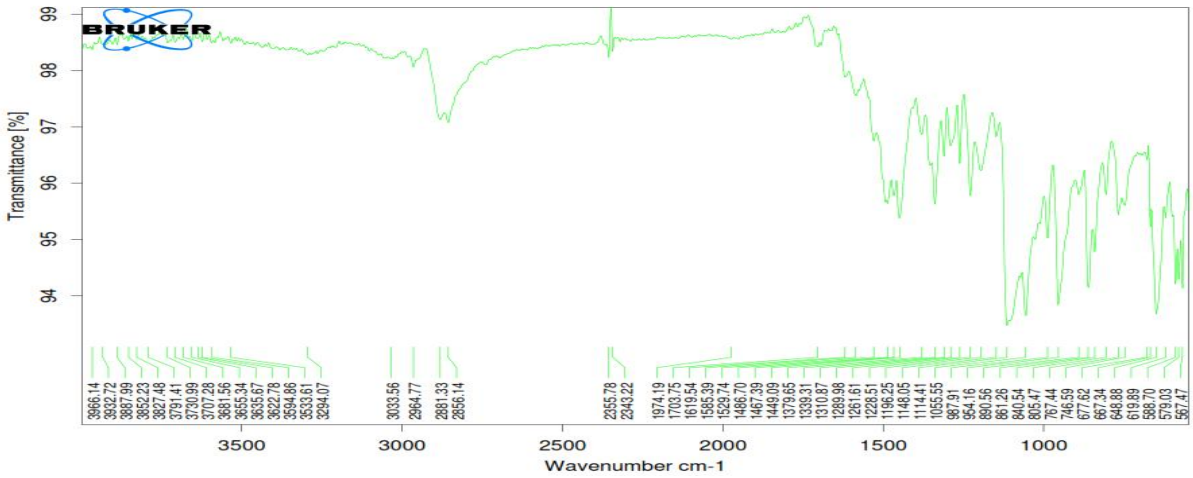


Fig 7.7: FTIR spectra of optimized formulation

From the above studies it was found that there was no shifting in the major peaks which indicated that there were no significant interactions occurred between the Cenobamate and excipients used in the preparation of different Cenobamate Immediate Release formulations. Therefore, the drug and excipients are compatible to form stable.

Formulations under study, The FTIR spectra of Cenobamate and physical mixture used for optimized formulation were obtained and these are depicted in above figures. From the FTIR data it was evident that the drug and excipients do not have any interactions. Hence, they were compatible.

VIII. CONCLUSION

The present study was successfully carried out to formulate and evaluate immediate release tablets of Cenobamate with the aim of achieving rapid onset of action and improved patient compliance. Various formulations were prepared using suitable super disintegrants and evaluated for pre-compression and post-compression parameters, all of which were found to be within the acceptable pharmacopoeial limits. Among the different formulations, the optimized batch exhibited excellent hardness, friability, drug content uniformity, and rapid disintegration with enhanced dissolution profile. Thus, the study concludes that immediate release tablets of Cenobamate can be effectively formulated using suitable excipients, offering a promising dosage form for the management of epileptic disorders requiring quick therapeutic action.

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